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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/585,817 | 06/01/2000 | Dale B. Schenk | 00209-US-NEW6 | 4693 |

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| EXAMINER | |
|---|---|
| NICHOLS, CHRISTOPHER J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1647 | |

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/585,817 | SCHENK, DALE B. | |
| | Examiner | Art Unit | |
| | Christopher Nichols, Ph.D | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11,14-16,19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,14-16,19 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *11,14-16,19 and 21-25* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Appeal Brief*

1. In view of the Appeal Brief filed on 14 November 2003, the Examiner reviewed the rejections made and found them to be insufficient to address the claims, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

2. To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

3. If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

### *Status of Application, Amendments, and/or Claims*

4. The replacement drawings filed 14 November 2003 are accepted.

5. Claims **1-10, 12, 13, 17, 18, 20,** and **26-57** have been cancelled. Claims **11, 14,** and **24** have been amended. Claims **11, 14, 15, 16, 19,** and **21-25** are under examination.

### *Information Disclosure Statement*

6. The information disclosure statement filed 11 May 2001 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for

consideration by the Office. The Information Disclosure Statement filed 11 May 2001 is missing page 2 of the list. Pages 1 and 3-10 have been taken into consideration and initiated by the Examiner. Applicant is hereby invited to provide page 2 of the Information Disclosure Statement and any references listed therein for consideration with the reply to this Office Action.

***Maintained Rejections And/Or Rejections***

7. The Rejection of claims **11, 14, 15,** and **16** under 35 U.S.C. §102(b) as set forth at pp. 9-10 ¶29 in the previous Office Action (25 July 2003) is *withdrawn* in view of Applicant's amendments (14 November 2003).

8. The Rejection of claims **11, 14, 15,** and **16** under 35 U.S.C. §102(b) as set forth at pp. 10 ¶30 in the previous Office Action (25 July 2003) is *withdrawn* in view of Applicant's amendments (14 November 2003).

9. The Rejection of claims **11, 14, 15,** and **16** under 35 U.S.C. §102(e) as set forth at pp. 10 ¶31 in the previous Office Action (25 July 2003) is *withdrawn* in view of Applicant's amendments (14 November 2003).

10. It is noted that Applicant has undertaken substantial amendments of related Applications on which Dr. Schenk is listed as an Inventor. Thus the Examiner hereby withdraws all previously made double patenting rejections and puts forth a new double patenting rejection to take the amendments into account. This is done in the interest of expedited prosecution (MPEP §707).

***Provisional Non-Statutory Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims **11, 14, 15, 16, 19,** and **21-25** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **11-25** of copending Application No. 09/724,575. While not identical, the claims of the instant application and Application No. 09/724,575 both encompass a method of treating a disease characterized by amyloid deposit in a patient, comprising administering an effective dosage of an agent that induces a salubrious immune response wherein said agent is PrP. Thus both applications jointly encompass the same invention. This is a provisional obviousness-type double patenting rejection.

***Maintained Rejections And/Or Rejections***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims **11, 14, 15, 16, 19,** and **21-25** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth at pp. 4-9 ¶11-27 in the previous Office Action (25 July 2003) and the new grounds of rejection as set forth herein.

13. The instant claims are drawn very broadly to a method of treating prion disease via active immunization with PrP or an active immunogenic fragment of PrP known as "AScr" which is synonymous with $PrP^{Sc}$ (pp. 20 of the Specification). The language of said claims encompasses all prion disorders which includes Creutzfeldt-Jakob disease (CJD), kuru, fatal familial insomnia, familial thalamic dementia, and Gerstmann-Sträussler-Scheinker disease (GSS).

14. The specification teaches that the administration of particular $A\beta_{42}$ (AN1792) fragments with an immunogenic adjuvant reduces β-amyloid levels within the brains of transgenic PDAPP mice. These mice exhibit Alzheimer type over production and build up of β-amyloid within the brain. However, as recognized in the art, these mice do not exhibit Down's Syndrome or other amyloidogenic diseases, see in particular Schenk *et al.* (1999) "Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse." Nature **400**:173-77 **(IDS#148)** and Games *et al.* (9 February 1995) "Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein." Nature **373**(6514): 523-527 **(IDS#109)**. Thus, the model system used in the instant Specification is not recognized as providing for teachings that are predictive of the results which would be expected for the full scope of the claims. For example, the art recognizes that such *in vivo* models are not readily

correlated to the human *in vivo* case. In particular, the art teaches a lack of correlation of beneficial effects shown in the mouse model system in humans; see in particular Münch & Robinson (July 2002) "Potential neurotoxic inflammatory responses to Aβ vaccination in humans." J. Neural Transmission 109(7-8): 1081-87 **(IDS#359)**.

15. In addition, administration of $A\beta_{42}$ to Alzheimer's patients is not predictive of how administration of PrP affects patients with prion-related diseases or any given amyloid dependent disorders. There are no examples directed to PrP, diseases caused by PrP, or art-accepted PrP animal models.

16. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed method of using PrP or AScr for active immunization in a patient to prevent a prion disorder. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known prion proteins, prion disorder signs and symptoms to correlate with treatment of said prion disorder. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

17. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a possibly toxic protein based solely on the performance of a different protein is highly problematic [see Weissman & Aguzzi (1997) "Bovine Spongiform encephalopathy and early onset variant Creutzfeldt-Jakob disease." Current Opinion in Neurobiology 7: 695-700 **(IDS#172)**]. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed method for treatment of prion diseases and/or disorders, such

a disclosure would not be considered enabling since the state of prion diseases and/or disorders is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

18. The following references are cited herein to illustrate the state of the art of *active* immunization and prion disease/disorders.

19. On the correlation between Aβ and PrP, the PDAPP mouse is a representative mouse model of Alzheimer's disease but not prion disorders {see Aguzzi & Weissman (23 October 1997) "Prion research: the next frontiers." Nature **398**: 795-798}. Furthermore, the skilled artisan must take the ancillary effects of the introduction of an immune response in a mammalian nervous system into consideration. The specification must establish that the antigens injection into the subjects produce a specific immune response and do not act as pyrogens (leading to cranial swelling for example). Due to the large quantity of experimentation necessary to evaluate all the effects of the difficulty of predicating an immune response in the nervous system, the lack of direction/guidance presented in the specification about collateral damage due to a vigorous immune response in an immunological privileged area (such as the nervous system), the absence of working examples directed to successful antigen presentation of a neurological protein, the complex nature of the invention, the unpredictability of the effects of antigens on the mammalian

nervous system, and the breadth of the claims which fail to recite limitations for what constitutes a successful, controlled immune response in the mammalian brain, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

20. Regarding the breadth of the claims, Goldfarb and Brown (1995) "The Transmissible Spongiform Encephalopathies." Annu. Rev. Med. **46**: 57-65 teaches that prion disease also known as transmissible spongiform encephalopathies (TSEs) encompasses kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and fatal familial insomnia (Abstract). All of these diseases share a common element of a prion protein however the diseases are caused by different mutations and various isoforms may or may not be infectious (Table 1 and Table 2). In addition, Kovács *et al.* (2002) "Mutations of the Prion Protein Gene." J. Neurol. **249**: 1567-1582 teaches that different mutations of the prion protein gene are responsible for different diseases with differing ages of onset and severity (Tables 1 and 2; Figures 4 and 5). Thus the skilled artisan is confronted with an undue burden of experimentation and unpredictability on how each individual isoform and/or mutation will affect the immune system of a patient [see also Elan Press Releases (1 March 2001 and 18 January 2002)].

21. Regarding derivatives and fragments of PrP (i.e. "components") encompassed by the claims, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure

and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly small peptides, conjugation appears to be required for promoting an effective immune response.

22. On the nature of the invention, Hsiao (1997) "From prion diseases to Alzheimer's disease." J Neural Transm Suppl. **49**: 135-144 teaches that Alzheimer's disease (AD) and prion diseases differ on the location of their pathogenesis and the protein which lead to their respective pathogenesis (pp. 137-138). The β-amyloid and the prion proteins are different as are the animals models used to study them. Thus it has not been established that AD animal models and data derived from them can translate to predictions on the success of prion proteins.

23. On the nature of the invention, Goldsby *et al.* (2002) Kuby Immunology Chapter 18 "Vaccines" (pp. 449-465) teaches that active immunization is not predictable as peptides are not generally immunogenic. Thus the skilled artisan is confronted with undue burden of experimentation to determine which PrP peptides are useful for practicing the invention as claimed.

24. On the state of the prior art, Smits *et al.* (1997) "Prion Protein and Scrapie Susceptibility." Vet. Quart. 19(3): 101-105 (**IDS#158**) and Aguzzi & Weissmann (23 October

1997) "Prion research: the next frontiers." Nature **389**: 795-798 suggest that one method of acquiring a prion-based disorder, such as Transmissible Spongiform Encephalopathy or Creutzfeldt-Jakob disease, may be the consumption or administration of a prion precursor protein, such as PrP, to an animal. Therefore, instead of eliciting a beneficial immune response to alleviate the PrP disorder, the administration of the PrP protein or fragment may cause a prion disorder.

25. Concerning the level of predictability in the art, Diomede *et al.* (1996) "Activation effects of a prion protein fragment [PrP-(106-126)] on human leucocytes." Biochem. J. **320**: 563-570 teaches that a fragment of PrP, residues 106-126 is toxic to neurons and astrocytes *in vitro* but stimulates neutrophils, monocytes, and lymphocytes, also *in vitro* (Figure 6). Thus PrP may be toxic to some cells but not to others. Also, Diomede *et al.* noted that immune cells may be able to survive the toxic effects of PrP because they are constantly dividing thus allowing for their numbers to be replenished following exposure to PrP (pp. 569). Thus the skilled artisan is confronted with an unpredictability of the effects of prion precursor protein and its fragments on cells.

26. On the level of predictability in the art, Harmeyer *et al.* (April 1998) "Synthetic peptide vaccines yield monoclonal antibodies to cellular and pathological prion proteins of ruminants." Journal of General Virology **79**(4): 937-945 teaches that immunization of mice with 16 synthetic peptides derived from PrP with an adjuvant yielded monoclonal antibodies which vary in their species specificity, Ig class, and strength of binding to PrP (Table 2 & 3; Figure 3). Thus the skilled artisan is left with additional experimentation for the skilled artisan to first make PrP

peptides, administer them, and then characterize the immunological response (production of antibodies) to determine which PrP peptides produce the desired effect.

27. The references and data in the instant Specification concerning Aβ are compelling although it was done in an art-accepted model for Alzheimer's disease. This is not the case with PrP. No nexus between PrP immunizations, whether passive or active, has been established with a prion disorder. Further, Brown *et al.* (June 1997) "PrP and β-Amyloid Fragments Activate Different Neurotoxic Mechanisms in Cultured Mouse Cells." European Journal of Neuroscience 9(6): 1162-1169 teaches that PrP and Aβ, although similar, exhibit fundamentally different neurotoxic effects on neurons (Table 2). Thus one cannot reliably use data from Aβ to predict the activity, mechanisms, or effects of PrP that may be used in active immunization.

28. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of practicing the claimed method as a means of prevention when only treatment was demonstrated as exemplified in the references herein. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of practicing the claimed method as a means of prevention when only treatment was demonstrated as exemplified in the references herein.

29. The rejection of claims **11, 14-16, 19,** and **21-25** under 35 U.S.C. §112 ¶1 is maintained.

***Summary***

30. Claims **11, 14, 15, 16, 19,** and **21-25** are hereby rejected.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
December 15, 2003

Gary L. Kunz
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